IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	FRANANO	Confirmation No.:	2612
Serial No.:	09/669,051	Art Unit:	1655
Filed:	September 24, 2000	Examiner:	Srivastava, Kailash C
For:	METHODS FOR TREATING AN ARTERY OR VEIN IN A HUMAN SUBJECT	Attorney Docket No.:	31110-0002

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R § 1.97(a)(4)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. §1.56 to inform the Patent and Trademark office of all references coming to the attention of applicants or their attorneys which are or may be related to patentability of the claimed invention, Applicant hereby directs the Examiner's attention to references BJ and BK, which are listed on the accompanying PTO Form 1449. Copies of references BJ and BK are submitted herewith. Applicant respectfully requests that the cited references be considered and made of record in the prosecution file of the instant application.

Reference BJ and BK were referred to in a Written Opinion mailed on July 25, 2005 in International Application No. PCT/US04/05192. A copy of the Written Opinion is submitted herewith.

CERTIFICATE OF FACSIMILE TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

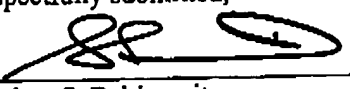
I hereby certify that this paper is being filed with the United States Patent and Trademark Office by facsimile transmission on January 19, 2006 to facsimile telephone number (571) 273-0923.

Stephen S. Rabinowitz (Reg. No. 40,286)

No fee is believed to be payable for this Information Disclosure Statement. If any fee is due, the Commissioner is authorized to charge the required fee to Fried, Frank, Harris, Shriver & Jacobson LLP Deposit Account No. 06-0920.

Respectfully submitted,

Date: January 19, 2006



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LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	ATTY DOCKET NO. 31110-0002	APPLICATION NO 09/669,051
	APPLICANT Franano	
	FILING DATE September 24, 2000	GROUP 1655

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

	BJ	Dobrin PB & Mrkvicka R, Cardiovasc. Surg. 2(4): 484-488 (1994)
	BK	Trubel W *et al.*, Eur. J. Vasc. Endovasc. Surg. 10: 415-423 (1995)

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

524016.1

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
LAURA A. CORUZZI
222 EAST 41ST STREET
NEW YORK, NY 10017-6702

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	25 JUL 2005
Applicant's or agent's file reference 11408-07-228	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/05192	20 February 2004 (20.02.2004)	20 February 2003 (20.02.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 38/48; C12N 9/66, 9/50; A61K 38/16; A61M 25/10 and US Cl.: 424/94.64, 94.67; 435/218, 219; 514/12; 604/509

Applicant

PROTEON THERAPEUTICS, LLC Response to Written Opinion Due 10/25/05

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Rosanne Kosson Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/05192

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/05192

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1,3,7,15-26,33-50 and 65-68

Form PCT/ISA/237 (Box No. IV) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/05192

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1,3,7,15-26,33-50 and 65-68	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1,3,7,15-26,33-50 and 65-68	NO
Industrial applicability (IA)	Claims 1,3,7,15-26,33-50 and 65-68	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1,3,7,15-26,33-50 and 65-68 lack an inventive step under PCT Article 33(3) as being obvious over Dobrin et al. (Cardiovasc Surg 2(4):484-488, 1994) in view of Wu et al. (US 5,712,247); Trubel et al. (Eur J Vasc Endovasc Surg 10(4) :415-423, 1995) and Tsukernik (US 6,494,861). Dobrin et al. disclose that inducing the degradation of elastin in arteries produces vessel dilation of 6-10% at 100 mm Hg, while inducing the degradation of collagen produces vessel dilation of 10-23% at 100 mm Hg (see p. 485, right column, p. 487, 1st and last paragraphs, and p. 488, last paragraph). Wu et al. disclose that increased amounts of elastase are released from neutrophils by contacting them with an agent such as LPS, TNF- α, or IL-8 (see col. 12, lines 24-33). Thus, to produce blood vessel dilation, it would have been obvious to one of ordinary skill in the art at the time that the invention was made to administer an agent that increases elastase release in blood vessels, such as LPS, TNF- α, or IL-8, because Wu et al. teach that these agents increase the amount of elastase in blood vessels and Dobrin et al. teach that when elastin in blood vessels is degraded, such as by the action of elastase, the blood vessels dilate.

Trubel et al. disclose that when two blood vessels of different diameters are joined by anastomosis, or when a blood vessel and a vascular graft of different diameter are joined by anastomosis (the grafts containing Dacron mesh), distal anastomotic intimal hyperplasia (DAIH) occurs. The degree of DAIH is proportional to the degree of mismatch in the diameters of the blood vessels, or blood vessel and graft, joined (see pp. 419-421). DAIH occludes the joined blood vessels. It would have been obvious to one of ordinary skill in the art to administer an agent that induces the release of elastase to a subject with a blood vessel occlusion resulting from a vascular graft or vascular anastomosis at the site of the blockage, because Dobrin et al. and Wu et al. teach that this agent produces blood vessel dilation. Trubel et al. teach that, in vascular anastomoses or vascular grafts with conduits of different diameters, intimal hyperplasia may result. The skilled artisan would have recognized that blockage in the occluded blood vessels or conduits could be relieved by administering an agent to this site that dilates the blood vessels, thereby restoring at least partial blood circulation.

Tsukernik discloses a device for and method of delivering a drug internally to a patient via a balloon catheter. The device can deliver the drug to locations in the vasculature, such as blood vessels or the heart, or to the urinary tract (the lumen of the urethra (see col. 3, lines 12-29, and col. 4, lines 28-29). The site to which the drug is delivered is controlled by positioning the balloon catheter. For controlling drug delivery, cycling of the pressure used to inflate the balloon is synchronized with cycling of the pressure that drives a syringe that infuses the drug (see col. 1, lines 9-19, and col. 4, lines 58-65). It would have been obvious to one of ordinary skill in the art to deliver a drug for dilating a blood vessel, such as the elastase-inducing agent taught by Dobrin et al. and Wu et al., by using the balloon catheter of Tsukernik, because Tsukernik teaches that this balloon catheter is designed for delivering cardiovascular and urinary tract drugs to a precise location in a patient.

Regarding claim 65, neutrophils may be found in conduits of the body other than blood vessels, such as in bronchi, particularly in the case of a subject suffering from a respiratory tract infection. In such a case, it would have been obvious to one of ordinary skill in the art to administer an agent that is an elastase inducer to dilate the bronchi so that the subject could breath more easily.

In view of the foregoing, the claims fail to satisfy the requirement of an inventive step.